CERVICAL DISEASE

Here's what you need to know about ACOG's latest guidelines on screening for cervical cancer

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"Astonishment fatigue." That phenomenon may be responsible for clinicians' muted reaction to new ACOG guidelines on cervical cancer screening, which were released late last year.[1] Through a coincidence of timing, the new guidelines hit the airwaves just after the U. S. Preventive Services Task Force announced controversial changes to its recommendations on mammography. As a result, the cervical cytology guidelines seemed to dissolve into the stratosphere.

Or, perhaps, the cervical cancer screening guidelines slipped by with little fanfare because they were soundly based in evidence and, therefore, widely accepted among ObGyns. Even if that is the case, the medical community may not be familiar with the specific data behind the guideline changes. In this article, I discuss the evidence driving all major changes to the guidelines based on Level-A evidence. Changes based on Level-B or -C evidence are listed in **TABLE 1**, page 24.

IN THIS ARTICLE

Hold off on cervical cancer screening until the patient is 21 years old

Screening before age 21 should be avoided because it may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer.[1]

How different is this from the 2003 ACOG recommendation to begin screening within 3 years of first intercourse or at age 21, whichever comes first?

Very, very different. In fact, it is **the most dramatic change in the 2009 screening recommendations.**

It is even more striking in comparison with ACOG's earlier recommendation—which prevailed from the late 1970s through 2002—to begin cervical screening at age 18 or at the onset of intercourse, whichever comes first.

The median age of first intercourse in the United States is 16 years. Until this latest change in guidelines, most young women began cervical screening during adolescence.

What's wrong with screening adolescents? Don't they acquire human papilloma-

TABLE 1 Other ACOG cervical disease guidelines are based on Level-B and Level-C evidence*

Recommendation	Level of evidence	Comment
Test sexually active adolescents (i.e., females 21 years or younger) for sexually transmitted infection, and counsel them about safe sexual practices and contraception	B	These measures can be carried out without cervical cytology and, in the asymptomatic patient, without the introduction of a speculum
It is reasonable to discontinue cervical cancer screening in any woman 65 to 70 years old who has had three or more consecutive negative Pap tests and no abnormal tests in the past 10 years	B	
Continue annual screening for at least 20 years in any woman who has been treated for CIN 2, CIN 3, or cancer. This population remains at risk of persistent or recurrent disease for at least 20 years after treatment and after initial posttreatment surveillance	B	
Continue to screen any woman who has had a total hysterectomy if she has a history of CIN 2 or CIN 3 or if a negative history cannot be documented. This screening should continue even after initial posttreatment surveillance	B	Although the screening interval may ultimately be extended, we lack reliable data to support or refute the discontinuation of screening in this population
Inform the patient that annual gynecologic examination may still be appropriate even if cervical cytology is not assessed at each visit	C	
Screen any woman who has been immunized against HPV 16 and 18 as though she has not been immunized	C	

* Level-B recommendations are based on limited and inconsistent scientific evidence. Level-C recommendations are based primarily on consensus and expert opinion.

virus (HPV)? (*Yes.*) And once they do, aren't they at risk of cervical cancer? (*Yes.*)

Several variables support the delay of screening to age 21:

- the transience of most HPV infections
- the typically long natural history of carcinogenesis in the few young women in whom HPV might persist
- the adverse consequences of overscreening and over-management of adolescents who have cervical intraepithelial neoplasia (CIN).

Let's look more closely at these variables.

HPV is common but usually resolves on its own

It's common for young women to acquire HPV shortly after they become sexually active, but their immune system clears most infections within 1 or 2 years without the virus producing neoplastic changes.[1]

HPV detection peaks in the late teens and early 20s, when approximately 25% of women test positive for the virus, resulting in high rates of low-grade squamous intraepithelial lesions (LSIL) and HPV-positive, atypical squamous cells of undetermined significance (ASC-US).[2] These findings are mostly transient.[2]

Detection of CIN 3 does not peak until a woman reaches her late 20s, and the median detection of microinvasive cancer does not peak until she reaches her early 40s. These facts indicate that adolescents have the lowest risk of incipient cervical cancer but the highest risk of undergoing unnecessary procedures for HPV-related events—events that are highly likely to resolve without treatment.

From 1998 to 2006, an average of 14 cervical cancers occurred annually in women 15 to 19 years old, an incidence of only 1 or 2 cases of cervical cancer for every 1 million women in that age group (**TABLE 2**).

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In teens, screening does not reduce mortality

Even this low rate of cervical cancer might justify the screening of adolescents, provided such screening was shown to reduce the incidence of and mortality from cervical cancer in that age group. However, all data point to the opposite conclusion:

- The incidence of cervical cancer in this age group has not changed since the years between 1973 and 1977, a period that preceded the recommendation to begin screening at age 18 or first intercourse
- No data demonstrate a benefit of screening in women younger than 21 years in regard to future rates of CIN 2 and 3—or even that screening women 20 to 24 years old reduces the rate of cervical cancer in women 30 years or younger[3]
- CIN 2 and 3 do occur in adolescents, and the fear of delaying their diagnosis has driven much of the opposition to the guideline change—specifically, the omission of the option to begin screening within 3 years after first intercourse; however, even when high-grade CIN develops, spontaneous regression is common in this age group (e.g., 65% rate of regression of CIN 2 after 18 months; 75% after 36 months)
- When CIN 3 develops and persists, more than 10 years are typically required for the lesion to acquire the capacity to become invasive.[1,2]

In addition, extensive data suggest that screening adolescents may be harmful. Adverse psychological effects related to cervical cancer screening, evaluation of abnormal results, and treatment of CIN have been reported, including negative effects on sexual function and a higher risk of preterm and low-birth-weight infants.[1]

Virtually all studies of pregnancy outcomes following loop electrosurgical excision procedure (LEEP) have demonstrated a doubling or tripling of the rate of preterm birth.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Screening women 21 years or younger for cervical cancer may be harmful and lacks proven benefit. Screening should not begin until the patient is 21, regardless of the age of first intercourse.

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TABLE 2 Incidence of invasive cervical carcinoma: United States, 1998-2003

Age (y)	Average annual count	Incidence (95% CI)	Incidence as a percentage	Median age at diagnosis
All ages	10,846	8.9 (8.8–9.0)	100	47
0–14	0	0	0	Not applicable (NA)
15–19	14	0.2 (0.1–0.2)	0.1	NA
20–24	123	1.6 (1.5–1.7)	1.1	NA
25–29	543	6.9 (6.7–7.2)	5.0	NA
30–34	1,045	12.3 (12.0–12.6)	9.6	NA
35–39	1,350	14.6 (14.3–14.9)	12.5	NA
40–44	1,534	16.3 (15.9–16.6)	14.1	NA
45–49	1,323	15.4 (15.0–15.7)	12.2	NA
50–59	1,958	14.5 (14.2–14.7)	18.0	NA
60–69	1,352	14.8 (14.5–15.1)	12.5	NA
70–79	1,008	12.9 (12.6–13.3)	9.3	NA
≥80	595	11.2 (10.9–11.6)	5.5	NA

Source: Watson et al[5]

Extend the screening interval to 2 years for women 21 to 29 years old

Both liquid-based and conventional methods of cervical cytology are acceptable for screening; hence, screening frequency should not vary based on the method used.[1]

The 2003 ACOG guidelines recommended annual cervical screening of women in their 20s using either conventional or liquid-based cytology. In contrast, in 2002, the American Cancer Society (ACS) recommended annual screening when the conventional Pap test was used, and a 2-year interval when screening involved liquid-based cytology. With ACOG's latest recommendation—a 2-year interval for women 21 to 29 years old, regardless of test method—the College moves in line with the ACS in regard to liquid-based cytology. It also acknowledges more recent evidence that liquid-based cytology is no more sensitive than conventional cytology.[1]

Liquid-based cytology does have a number of other unquestionable advantages, however:

- It offers the convenience of being able to test for HPV, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* directly from the residual sample
- It produces fewer unsatisfactory cytology results than conventional cytology
- Cytotechnologists find liquid-based cytology easier to read.

More than 90% of Pap tests in the United States utilize liquid-based cytology, and that percentage is not likely to diminish.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Women 21 to 29 years old should have a Pap test every 2 years, regardless of the method used.

FAST TRACK

Liquid-based cytology is easier to read and produces fewer unsatisfactory cytology results than conventional Pap testing

Some women 30 years and older can be screened every 3 years

Cervical cytology screening is recommended every 3 years for women age 30 years and older if:

- *they have had three consecutive negative cervical cytology screening test results and have no history of CIN 2 or CIN 3, are not HIV-infected, are not immunocompromised, and were not exposed to diethylstilbestrol in utero or*
- *they have received negative test cotest results on both cervical cytology screening and HPV DNA testing and are considered low risk.*[1]

A study of the detection of squamous cell cervical cancer (SCC) within 3.5 years of one, two, or three consecutive normal Pap tests demonstrated that the incidence of cervical cancer increases to 3 to 5 cases for every 100,000 woman-years in each of the subsequent 2 years. Some experts argue that this relatively low increase—the equivalent of the incidence of breast cancer in men—supports extension of the screening interval to 3 years after three consecutive normal Pap results.

Clinicians have generally been hesitant to widen the screening interval, despite ACS and ACOG recommendations for 2- or 3-year screening among women who have had three consecutive normal results. Many of these clinicians may find it difficult to dismiss even this low number of excess cancers (3 to 5 cases for every 100,000 woman-years) when more frequent or better screening

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would likely prevent them. As a result, the extension of screening intervals on the basis of negative cytology alone may continue to meet resistance from clinicians and their patients.

Wider intervals reduce the risk of unnecessary treatment

The extension of screening intervals, whether it is based on cytology alone or cytology combined with HPV testing, benefits most women by reducing the likelihood that transient, HPV-induced events will be detected and treated even though they are not destined to become CIN 3, adenocarcinoma in situ, or cervical cancer.

At the same time, however, extending the screening interval to 3 years in the setting of "opportunistic" screening—the screening approach used in the United States—may lead to irregular screening for many women at intervals beyond the recommended 3 years, thereby reducing the protective effect of a program based on cytology alone. Approximately 10% of cervical cancers occur in women who have not had a Pap test in the preceding 5 years.

Cotesting may be the solution

There is no question that extending cytology-only screening beyond 3 years significantly increases the risk of cervical cancer. However, among women tested for HPV, the risk of CIN 3 or greater does not begin to rise until at least 6 years following a negative test result, providing a margin of safety that would protect most women who miss the recommended 3-year screening interval.

Earlier this year, Ronco and colleagues published the results of a large primary cervical screening trial involving more than 94,000 women who were randomly assigned to screening with cytology alone or cotesting (i.e., cytology plus HPV testing).[4] In the cytology-only group, women were referred to colposcopy for a Pap result of ASC-US or higher-grade findings. In the cotesting group, they were referred to colposcopy if the HPV or Pap test (or both) was positive. A second screening was performed an average of 3 years later, and the incidences of CIN 2, CIN 3, and cancer at each screening were compared between groups.

The number of cancers detected in the initial round of screening did not differ between groups. In the second round of screening, no cancers were found in the cotesting group, compared with nine cancers in the cytology-only group. The authors attributed this difference to the detection and treatment of twice as many cases of CIN 3 in the initial round of screening among women undergoing cotesting, compared with those tested with cytology alone.[4]

In addition, women in the cotesting group had an extremely low rate of CIN 3 in the second round of screening (2 cases for every 10,000 women). Investigators also noted that a high proportion of invasive cancers detected in the cytology group during the second round of screening were adenocarcinomas, consistent with reports from earlier studies that found cytology to be less effective in detecting adenocarcinomas than in detecting SCC.[4]

Although HPV testing was previously shown to outperform cytology in reducing the risk of cervical cancer in a low-resource country (India), this is the first study to do so in a developed country with a well-screened population and a low incidence of cervical cancer.[4]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although ACOG guidelines encourage the extension of screening intervals to 3 years for women 30 years or older who have had three consecutive normal Pap tests, many clinicians have been reluctant to take this step. Cotesting with HPV and Pap tests should provide the reassurance necessary for these clinicians to adopt the wider screening intervals.

FAST TRACK

When the Pap and HPV tests are performed simultaneously (cotesting), the screening interval can be safely extended to at least 3 years for women who have negative results on both tests

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Keep annual screening for women who have a history of CIN, HIV, or certain chronic conditions

The recommendations to screen women every 2 years until age 30 and to extend the screening interval to 3 years thereafter, provided three consecutive Pap tests are normal or cotesting is negative, apply only to women at average risk of cervical cancer. Conditions that indicate elevated risk include:

- HIV infection
- immunosuppression for other reasons, e.g., organ transplant
- in utero exposure to diethylstilbestrol
- history of CIN 2, CIN 3, or cancer.

Two Pap tests are recommended in the first year after diagnosis of HIV infection, followed by annual screening. It can be presumed that women who have chronic immunosuppression should be managed similarly.

As for women known to have been exposed to diethylstilbestrol in utero, no specific recommendation is given other than "more frequent screening."[1]

The relatively recent documentation that women with a history of CIN 2 or 3 (and probably adenocarcinoma in situ) remain at risk of developing cervical cancer for at least 20 years after treatment warrants annual screening for at least 20 years. The increased reassurance that no CIN 3 or greater is missed when cotesting is negative for both cytology and HPV testing might argue for extension of the screening interval for women who have negative cotest results and who have completed recommended posttreatment follow-up. However, at this time, we lack data on long-term follow-up of women who have been treated for cervical neoplasia and who have negative cotest results. Therefore, such a recommendation cannot be made at this time.

When can screening be discontinued?

Routine cytology testing should be discontinued after total hysterectomy for benign indications, provided the woman has no history of high-grade cervical intraepithelial neoplasia or adenocarcinoma in situ.[1] This recommendation has not changed since the 2003 ACOG guidelines on cervical cancer screening were published, and it is consistent with guidelines from the U.S. Preventive Services Task Force and the American Cancer Society.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Do not increase the screening interval beyond annual testing for women who are HIV-positive, who are immunosuppressed, who were exposed in utero to diethylstilbestrol, or who have been treated for CIN 2 or 3 or adenocarcinoma in situ.

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